IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Stanka PERC et al. Serial No.: 10/531,540 Filed: April 15, 2005 For: Pharmaceutical Formulation of Olanzapine	Examiner: Samira JM, Jean-Louis Group Art: 1627

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APPELLANT'S REPLY BRIEF

SIR:

This is Appellants' Reply Brief in response to the Examiner's Answer mailed August 17, 2010, pursuant to 37 C.F.R. § 41.41.

The Examiner maintains the rejection of claims 34-51 under 35 U.S.C. 103 § (a) as obvious over Morris et al. (EP 0 830 858 A1) ("Morris") as evidenced by Nakajima et al. (U.S. 3,926,817), and the rejection of claims 34-51 under 35 U.S.C. 103 § (a) as obvious over Chakrabarti et al. (U.S. 5,229,382) ("Chakrabarti") in view of Rubinstein et al. (Pharmaceutics: The Science of Dosage Form Design, 1988, Tablets, Chapter 18, pgs. 304-321) ("Rubinstein").

In response to Appellant's Appeal Brief, at pages 12-18, section 10 of the Examiner's Answer, the Examiner ex plains why the rejections should be maintained. For reasons expressed

below, it is believed that the Examiner fails to properly apply the pertinent laws, rules, and guidance in applying the prior art against the preset application.

Claim 34 is the only independent claim and defines a pharmaceutical formulation comprising a **homogeneous** mixture of: (a) **uncoated** olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient; (b) a monosaccharide and/or oligosaccharide and/or a reduced or oxidized form thereof; (c) a polysaccharide; and optionally, d) one or more additional excipients.

In this Reply Brief, Appellants address the statements made by the Examiner in section 10 of the Examiner's Answer.

I. Claims 34-51 are patentable under 35 U.S.C. § 103(a) over Morris as evidenced by Nakajima

1. Obviousness is not appropriate when the proposed combination requires a greater expenditure of time, effort, or resources than the prior art teachings

To render claims 34-51 obvious over Morris, the Examiner speculates that it would have been obvious for a person of ordinary skill in the art to formulate uncoated olanzapine, if the desire is to rapidly consume such formulation. Appellants have previously explained why a person of ordinary skill in the art would not do so. For example, if one would use uncoated olanzapine for rapid consumption, as suggested by the Examiner, s/he should at least warn physicians and patients that the uncoated olanzapine product should be consumed as soon as possible after the package is opened. In case that the package is opened and the product is not used up immediately, the unused product will have to be abandoned due to the occurrence of discoloring. Alternatively, one may consider placing only one unit dosage of tablet(s) in an amber, high density polyethylene bottle for

one-time use, which will unduly increase the manufacturing cost and be unacceptable to a manufacturer. Also, because uncoated olanzapine is so sensitive to the open air, as taught in Morris, various precautions should be adopted to make sure that the uncoated olanzapine formulation is packaged well and tight, therefore resulting in increased cost. In any case, the use of uncoated olanzapine, as proposed by the Examiner, is impractical. Therefore, in view of these problems and difficulties associated with uncoated olanzapine, as suggested by Morris, a person of ordinary skill in the art would not use any uncoated olanzapine for any use, even for rapid consumption, as suggested by the Examiner.

Moreover, Morris taught that coated olanzapine tablets do not have any of the problems associated with uncoated olanzapine tablets. Therefore, one would use coated olanzapine tablets for both normal use and "rapid consumption" as proposed and speculated by the Examiner. *See* also MPEP 2145X. D.3 ("The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).") In other words, if there is a better, more practical solution, without any particular reason, why would a person of ordinary skill in the art formulate an impractical olanzapine formulation and then package only one dosage of olanzapine formulation in one amber, high density polyethylene bottle for one time use?

In response, the Examiner argues in the Examiner's Answer "[O]bviousness does not hinge on whether better choices existed but rather whether such formulation can be reasonably made and be made successfully" and "[A] *prima facie* case of obviousness does not hinge on marketing cost or desirability but is rather governed by the teaching or suggestion of the prior art and if there is reasonable expectation of success." *See* page 13, first full paragraph and page 15, first full paragraph of the Examiner's Answer. But the Examiner fails to cite to any legal

authority to support these statements. In fact, the Examiner's statements violate the principles enunciated in relevant cases and the PTO's guidelines.

Specifically, at PTO's recent "Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex", Federal Register, Vol. 75, No. 169, page 53646, middle column, first full paragraph (September 1, 2010) ("PTO Guidelines Update"), the PTO emphasizes:

> In view of the cases decided since *KSR*, one situation when it is important to identify a reason to combine known elements in a known manner to obtain predictable results is when the combination requires a greater expenditure of time, effort, or resources than the prior art teachings. **Even though the components are known, the combining step is technically feasible, and the result is predictable, the claimed invention may nevertheless be nonobvious when the combining step involves such additional effort that no one of ordinary skill would have undertaken it without a recognized reason to do so.** When a combination invention involves additional complexity as compared with the prior art, the invention may be nonobvious unless an examiner can articulate a reason for including the added features or steps. This is so even when the claimed invention could have been readily implemented.

(Emphasis added.)

As is clear from the above PTO guidelines, merely showing that the proposed combination "can be reasonably made and be made successfully," as argued by the Examiner, is not sufficient. The Examiner must articulate a particular reason why a person of ordinary skill in the art would use uncoated tablets for rapid consumption, which, based on Morris and as discussed above, would amount to extra work, effort, and greater expense, compared to the use of coated tablets for rapid consumption.

At page 53646, paragraph bridging middle and right columns, the PTO Guidelines Update continues to explain: "Even where a general method that could have been applied to make the claimed product was known and within the level of skill of the ordinary artisan, the claim may nevertheless be nonobvious if the problem which had suggested use of the method

had been previously unknown." Here, as explained in the previously submitted Appeal Brief, Morris fails to recognize that the use of a **homogeneous** mixture of **uncoated** olanzapine with polysaccharide, etc. can solve the undesirably discoloring problem. Rather, Morris suggests that using uncoated olanzapine will cause discoloring.

2. Morris teaches away from uncoated olanzapine formulation

As explained in Appellants' previously submitted Appeal Brief, Morris teaches away a person of ordinary skill in the art from making an uncoated olanzapine formulation, because according to Morris, leaving olanzapine uncoated would result in undesirable color change and appearance; and it is particularly so considering that the olanzapine formulation would be used for a patient suffering from hallucinations, delusions, and being out of touch with reality. Due to olanzapine's known moisture sensitive, metastable nature in the art, a person of ordinary skill in the art would formulate an olanzapine formulation very carefully, and try to develop a pharmaceutically elegant granule formulation. *See* Morris, page 2, lines 6-10, and Chakarabarti, col. 11, Example 4. Without knowing the surprising discovery by the present inventors, a person of ordinary skill in the art would not simply mix olanzapine with other excipients evenly to make a homogenous mixture, by e.g., direct compression.

But the Examiner continues to argue "[I]f the desire is to provide a formulation of olanzapine that is rapidly consumed or consumed within 5 days, then one of ordinary skill in the art would have indeed found it obvious to formulate an uncoated olanzapine formulation." *See* page 13, first full paragraph of the Examiner's Answer. The Examiner's argument lacks merits.

As stated in *In re Sullivan,* 498 F.3d 1345 (Fed. Cir. 2007) (quoted by PTO's Guidelines Update, pp. 53657-53658), all evidence must be considered, including "a statement of intended use." As disclosed in Morris, olanzapine is known for treating patients suffering psychotic

conditions, such as hallucinations, delusions, and loss of touch with reality; and it is desired that an olanzapine product after being exposed to the air have long-term stability. That is why Morris proposes a pharmaceutically elegant solid oral formulation comprising olanzapine coated with certain polymers. *See*, e.g., the abstract, page 2, lines 14-18 and 35-51. Therefore, there is no basis for the Examiner's proposed modification of uncoated tablets of Morris for rapid consumption. Nor does the Examiner provide any evidence that there is a recognized use of olanzapine tablets for rapid consumption in the art.

The Examiner again states: "[F]indings by the EPO and WIPO have no bearings on U.S. Patent Laws." *See* page 16, lines 6-8 of the Examiner's Answer. Appellants have never disputed this statement. But Appellants refer to WIPO's findings to show how a person of ordinary skill in the art would understand Morris, the differences between Morris and the present invention, and whether the results of the present invention would have been unexpected from Morris. Indeed, WIPO's understanding about Morris is consistent with Appellants' position that Morris fails to teach a formulation comprising uncoated olanzapine and in fact teaches away from such a formulation.

Additionally, according to Morris, when exposed to open air ambient conditions, the uncoated tablets discolor **within (not until or by)** 5 days. In other words, according to Morris, uncoated olanzapine may discolor **any time**, but by no later than 5 days, after exposure to the ambient conditions. Therefore, the uncoated olanzapine formulation cannot be satisfactorily used for rapid consumption within 5 days as stated by the Examiner (i.e., the user can use the product any time within 5 days, e.g., 1 day, 2days, or 5 days after the product is exposed to air), because during these 5 days the uncoated olanzapine formulation may have discolored before it is consumed by patients.

3. The beneficial results of the present invention would indeed have been unexpected

In response to Appellants' previous arguments that the Examiner fails to evaluate the unexpected results of the present invention, the Examiner now states: "[T] instant invention is neither unexpected nor unobvious in light of the disclosure of Morris" because "Nowhere in the claims has appellant recited a limitation for stability nor has appellant defined a threshold for what a stable composition is supposed to be." *See* pages 15-16, bridging paragraph of the Examiner's Answer. The Examiner's argument lacks merits.

First, the law does not require that "unexpected results" of a claimed invention be recited in the claims. In contrast, "a claim covers and secures a process, a machine, a manufacture, a composition of matter, or design, but never the function or result of either, nor the scientific explanation of their operation." *See Markman v. Westview Instruments, Inc.*, 116 S.Ct. 1384, 1388 (1996). Therefore, the fact that the claims of the present application do not recite the stability of the claimed formulation does not provide a valid basis for the Examiner not to consider unexpected results of the present invention.

Second, as discussed above, based on Morris, a person of ordinary skill in the art would expect that a formulation containing uncoated olanzapine would discolor any time but by **not later than 5 days** after the tablets are exposed to air under room temperature and 40% relative humidity. *See* page 4, lines 45-48 of Morris. In contrast, Appellants surprisingly discovered that a tablet formulation comprising a homogeneous mixture of uncoated olanzapine and other excipients in accordance with the present invention has a good stability. For example, Example 3 of the present application shows that an uncoated olanzapine formulation made in accordance with an embodiment of the present invention is stable under accelerated stability study conditions, i.e., 40^0C and 75% relative humidity, for **at least 6 months**. A person of ordinary

skill in the art would by no means reasonably expect based on Morris the surprising discovery of the present invention before the filing of the present application.

Based on the foregoing and the reasons provided in Appellants Appeal Brief, claim 34 is not obvious under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima. For at least the same reasons, none of claims 35-51, each of which depends from claim 34, is obvious under 35 U.S.C. §103(a) over Morris and Nakajima.

II. Claims 34-51 are patentable under 35 U.S.C. § 103(a) over Chakrabarti in view of Rubinstein

Claims 34-51 stand rejected as being unpatentable over Chakrabarti in view of Rubinstein under 35 U.S.C. §103(a). Appellants respectfully traverse.

1. The Examiner fails to articulate any reason why a person of ordinary skill in the art would disregard the specific granulating technique disclosed in Chakrabarti and select the technique of "direct compression" from among many other conventional techniques disclosed in the secondary reference Rubinstein to arrive at the present invention

Chakrabarti discloses preparing an olanzapine formulation by process of granulating, which does not lead to a homogenous mixture. The Examiner previously argued that Chakarabarti discloses the use of conventional techniques for the preparation of olanzapine formulation and therefore discloses a homogenous mixture of olanzapine. In response to Appellants' statement that the Examiner fails to identify which specific "conventional" technique a person of ordinary skill in the art would choose for the preparation of olanzapine formulation, the Examiner now argues that this person would choose 'direct compression" from various conventional techniques disclosed in the secondary reference Rubinstein. But the Examiner still fails to articulate a reason why a person of skilled in the art would disregard specific granulating technique disclosed in Chakrabarti and select the technique of "direct compression" from among

many other conventional techniques disclosed in Rubinstein to arrive at the present invention. *See In re Fritch*, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992) (The mere fact that the prior art could be modified would not have made the modification obvious **unless the prior art suggested the desirability of the modification.**)

As stated in Appellants' previously submitted Appeal Brief, at col. 8, lines 16-46, Chakrabarti broadly discloses that conventional techniques may be used to prepare a formulation, which can be in the form of **tablets, capsules, injection solution, suspension, suppositories, and sachets**. But nowhere does Chakarabarti disclose the use of direct compression or any other method to make a homogenous mixture. Rather, Charkarabarti specifically discloses the use of granulation, which is the most widely used conventional technique but cannot produce a homogeneous mixture. This is understandable, because as noted above, due to olanzapine's known moisture sensitive, metastable nature in the art, a person of ordinary skill in the art would formulate olanzapine formulation very carefully, and try to develop a pharmaceutically elegant **granule** formulation. *See* Morris, page 2, lines 6-10, and Chakarabarti, col. 11, Example 4. Without knowing the surprising discovery by the present inventors, a person of ordinary skill in the art would not **simply** mix olanzapine with other excipients evenly to make a homogenous mixture by, e.g., direct compression. *See* also MPEP2144.04 ("Note that the omission of an element and retention of its function is an indicia of unobviousness.")

Moreover, the unexpected results of the present invention as discussed above also show that claim 34 is not obvious under 35 U.S.C. §103(a) over Chakrabarti and Rubinstein. A person of ordinary skill in the art would not expect from Chakrabarti and Rubinstein that an olanzapine formulation, which, for example, can remain stable under 40^0C and 75% relative humidity for at

least 6 months, such as the composition of Example 3 of the present application, can be prepared by a simple direct compression process, without any need for coating or wet granulation.

For at least the same reason, none of claims 35-51, each of which depends from claim 34, is obvious under 35 U.S.C. §103(a) over Chakrabarti and Rubinstein.

Based on the foregoing and the reasons discussed in Appellants' previously submitted Appeal Brief, reversal of the rejection of claims 34-51 under 35 U.S.C. §103(a) over Chakrabarti and Rubinstein is respectfully requested.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that Appellants' claims are not rendered obvious and are, therefore, patentable over the art of record, and the Examiner's rejections should be reversed.

Respectfully submitted,
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